

High Sensitivity Cardiac Troponin and New Onset Heart Failure: A Systematic Review and Meta-Analysis of 67,063 individuals with 4,165 incident heart failure events

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Abstract

Background: Identification of individuals at high risk of heart failure and early risk factor modification with medications such as ACE inhibitors may delay the onset of heart failure. High-sensitivity cardiac troponin (hs-cTn) has been suggested as a prognostic marker for the incidence of first-ever heart failure in asymptomatic individuals.

Methods: Pubmed, Embase and Web of Science were systematically searched for prospective cohort studies published before January 2017 that reported associations between hs-cTn and incident heart failure in individuals without baseline heart failure. Study-specific multivariable adjusted hazard ratios were pooled using random-effects meta-analysis.

Results: Data were collated from sixteen studies with a total of 67,063 individuals and 4,165 incident heart failure events. Average age was 57 years and 47% were female. Study quality was high (Newcastle-Ottawa score: 8.2/9). In a comparison of participants in the top third with those in the bottom third of baseline values of hs-cTn, the pooled multivariable adjusted hazard ratio for incident heart failure was 2.09 (95% CI 1.76-2.48, $p < 0.001$). Between-study heterogeneity was high with an I^2 of 80%. Hazard ratios were similar in men and women (2.29 [1.64-3.21] vs 2.18 [1.68-2.81]), with hs-cTnI and hs-cTnT (2.09 [1.53-2.85] vs 2.11 [1.69-2.63]) and across other study-level characteristics. Further adjustment for B-type natriuretic peptides yielded a similar hazard ratio of 2.08 (1.64-2.65). Assay of hs-cTn in addition to conventional risk factors provided improvements in the c-index of 1-3%.

Conclusions: Available prospective studies indicate a strong association of hs-cTn with the risk of first-ever heart failure and significant improvements in heart failure prediction.

Introduction

Cardiac troponins are structural proteins in the contractile apparatus of the myocyte.

Upon myocardial damage, they are released into the circulation (1) and they are therefore central in the diagnosis of myocardial infarction (2). Measurement of cardiac troponin with early assays was considered as a dichotomous test, classifying patients as being positive or negative for myocardial infarction. The advent of high-sensitivity cardiac troponin (hs-cTn) assays in recent years has changed this paradigm. High-sensitivity assays have allowed cardiac troponin to be considered as a quantitative measure of cardiac myocyte injury in the setting of myocardial infarction, and can measure cardiac troponin at low concentrations in individuals without myocardial infarction, where it can be regarded as a marker for myocardial stress (2,3).

We have previously demonstrated in a meta-analysis of 29 studies that cardiac troponin concentration in people without manifest cardiovascular disease (CVD) is associated with the long-term risk of developing coronary heart disease or stroke (4). In addition to these two outcomes, hs-cTn may also be a prognostic marker for the development of heart failure (HF). Identification of better prognostic marker for incident HF is important because HF is associated with poor survival, reduced quality of life, and significant healthcare costs (5). Furthermore, as reported by a recent UK-based study, HF has become the most common initial presentation of CVD (6). Still, prediction models aiming to identify individuals at high risk of HF are currently not included in CVD prevention guidelines (7,8) and are not established in clinical practice (9). The potential of cardiac biomarkers in HF prediction is exemplified by a meta-analysis showing natriuretic peptides improve risk discrimination and classification in general population studies (10). Risk scores for HF could help target preventive medication, such as statins

(11), intensive blood pressure control (12), and angiotensin-converting-enzyme inhibitors (13).

The aim of this study was to systematically collate and appraise the available evidence regarding the association between hs-cTn and incident HF and the added value of hs-cTn in HF prediction.

Methods

This systematic review is reported in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guideline (14) and the protocol was registered prospectively with PROSPERO (CRD42017054828).

Literature search

Electronic searches of Pubmed, Embase and Web of Science were performed on 3rd January 2017 (search strategy detailed in Supplementary table 1) with no filters or language restrictions applied. This was supplemented by review of relevant conference proceedings (i.e. American Heart Association Scientific Sessions, American College of Cardiology Sessions, European Society of Cardiology Annual Congress from 2014-2016) and of reference lists of identified studies. The searches were conducted by two independent investigators (J.E. and S.D.) and any discrepancies were resolved, by consensus, with a third investigator (S.P.).

Study eligibility criteria

To be eligible for inclusion, studies were required to: (i) have a prospective study design, including studies nested in randomized controlled trials; (ii) have enrolled individuals without HF at baseline; (iii) had measured high-sensitivity cardiac troponin; and (iv) had

recorded incident HF events over at least 1 year. Studies were excluded which involved patients in the early phase after acute myocardial infarction, undergoing cardiotoxic chemotherapy or with established myocardial or multisystem disease (e.g. sarcoidosis, amyloidosis).

Data extraction

Using a pre-specified data collection sheet, data were collated on population type (general vs high-risk populations), mean age, sex, ethnicity, baseline history of hypertension, diabetes, and CVD, hs-cTn assay type and manufacturer, number of participants, duration of follow-up and number of incident HF events. Furthermore, we assessed quality of included studies using the Newcastle-Ottawa tool for cohort studies (15), which considers participant selection, exposure measurement, ascertainment of outcomes, covariate adjustment, and adequacy of follow up. We also recorded which methods studies used to record incident HF events and how they defined them (fatal, non-fatal, or both). Hazard ratios for the association between hs-cTn and incident HF were extracted with the following levels of covariate adjustment, where available: (1) unadjusted or adjusted only for age and sex, (2) adjusted for demographic factors, conventional CVD risk factors and/or biomarkers other than natriuretic peptides, (3) adjusted for demographic factors, conventional CVD risk factors, non-natriuretic peptide biomarkers and natriuretic peptide levels. Where reported, C-indices as a measure for risk discrimination were extracted for predictive models with and without hs-cTn assessment.

Statistical analysis

All statistical analyses were performed using Stata Version 13 (StataCorp, USA) and a 2-sided p-value of <0.05 was deemed to represent statistical significance in the primary

analysis and <0.01 in meta-regression analyses due to multiple testing. Studies reported hazard ratios in different ways. These included a hazard ratio describing those above and below a specific threshold, between top and bottom quartiles or quintiles, per unit increase or per standard deviation increase in hs-cTn. In order to allow direct comparison of study specific hazard ratios, hazard ratios were transformed to represent the hazard ratio for the top third versus the bottom third of hs-cTn concentration within a given study. This transformation was performed under the assumption that the exposure variable is normally distributed and a log-linear association between exposure and outcome, as previously described (16,17). When estimates were presented both by groups of cardiac troponin as a categorical variable and as a continuous measure, the continuous measure was used as this is more compatible with the linear assumption used when transforming hazard ratios.

For the primary analysis, the most adjusted study-specific hazard ratios for the association between hs-cTn and incident HF were pooled by random effects inverse-variance weighted meta-analysis using the method of DerSimonian and Laird (18). This random-effects method was selected *a priori* due to a degree of anticipated heterogeneity in the populations studied and the design of included studies. Between-study heterogeneity was quantified using the I^2 statistic (19).

Secondary analyses pooled sex-specific hazard ratios using data from studies that reported associations separately in both men and women and compared hazard ratios according to the three pre-specified levels of covariate adjustment. Furthermore, meta-regression was used to test whether associations differed according to study-level characteristics. For categorical study-level characteristics, pooled hazard ratios were calculated within each subgroup. For continuous variables, study-specific estimates of

the association between hs-cTn and HF were plotted against the value of the variable of interest and a regression line fitted. The presence of publication bias was assessed with funnel plots and Egger's test (20).

Results

Summary of included studies

Electronic searches yielded 2,982 unique citations (**Figure 1**). Shortly after the date of the electronic searches, full text manuscripts of two abstracts identified in the search process were published and included (21,22). Data from 16 unique studies (21-35), reporting data regarding 67,063 participants with 4,165 first HF events, were included in this review. The included studies are summarized in **Table 2**. Ten studies included a sample of the general population and six comprised high-risk populations with either stable CVD, type II diabetes, chronic kidney disease or hypertension. All were prospective cohort studies; four were nested within randomized controlled trials. Seven studies were conducted in North America, five in Western Europe, two in East Asia, and two across multiple continents. All studies excluded individuals with a diagnosis of HF at baseline. Okuyama *et al* additionally excluded individuals with a left ventricular ejection fraction <50%; McQueen *et al* and Omland *et al* excluded those known to have a left ventricular ejection fraction <40%. Eight studies used HF hospitalization alone as the endpoint, four used all fatal or non-fatal HF diagnoses/events and two reported all non-fatal HF diagnoses/events. Overall, the quality of the included studies was good. Three studies fulfilled all nine elements of the Newcastle-Ottawa score, with the other 13 fulfilling eight of the nine criteria. The individual elements and overall Newcastle-Ottawa scores are shown in **Supplementary Table 5**. More detailed descriptions of the study population, method of follow up, outcome definitions, covariate adjustment and

details of the cardiac troponin assays used are reported in the appendix (**Supplementary Tables 2-4**).

Association of high-sensitivity cardiac troponin with incident HF

The pooled hazard ratio for incident HF comparing individuals in the top third versus those in the bottom third of hs-cTn concentration was 2.09 (95% confidence interval: 1.76-2.48, $p < 0.0001$, **Figure 2**). There was evidence of significant heterogeneity with an I^2 (95% CI) of 80 (68-87) %. The pooled hazard ratio was not materially changed upon further adjustment for B-type natriuretic peptide levels on top of CVD risk factors (**Figure 3**).

Sensitivity analysis using meta-regression confirmed that none of the categorical or continuous study level variables assessed were associated with differences in the hazard ratio for the association between hs-cTn and incident HF (**Figure 4** and **Supplementary Figure 2**). Pooled hazard ratios were 2.29 (1.64-3.21) in men, 2.18 (1.68-2.81) in women, 2.09 (1.53-2.85) with hs-cTnI, and 2.11 (1.69-2.63) with hs-cTnT. There was some evidence for publication bias on inspection of the funnel plot with two smaller studies reporting hazard ratios greater than the pooled estimate (**Supplementary Figure 3**), but the Egger's test was non-significant ($p = 0.126$).

Association of high-sensitivity cardiac troponin with heart failure subtypes

Two studies reported associations between hs-cTn and heart failure with preserved (HFpEF) and reduced ejection fraction (HFrEF) separately. In the PREVEND study, the hazard ratio for those with hs-cTnT in the top versus bottom third was greater for HFrEF (HR 1.79 (1.55-2.07)) than HFpEF (HR 1.30 (1.07-1.50)) (24). In the Cardiovascular Health Study, in those without left ventricular hypertrophy by echocardiography at

baseline, the corresponding hazard ratios were 2.70 (1.64-4.40) for HFrEF and 1.85 (1.30-2.68) for HFpEF (36). No studies reported data regarding heart failure with mid-range ejection fraction.

Association of changes in hs-cTn and incident heart failure

Two studies reported the association between changes in hs-cTn over time and incident heart failure. In the Cardiovascular Health Study, in those with a detectable hs-cTnT at baseline, the hazard ratio associated with a >50% increase 2-3 years later was 1.61 (1.32-1.97) after adjusting for conventional CVD risk factors. In the Atherosclerosis Risk in Communities Study, the corresponding hazard ratio for a >50% change in hs-cTnT at six years was 1.64 (1.39-1.95) (37). In those with undetectable hs-cTnT (<5ng/L) at baseline, a detectable value (>5ng/L) at six years was associated with a hazard ratio of 1.96 (1.62-2.37) (37).

Incremental discrimination with addition of hs-cardiac troponin

Eight studies reported improvements in the c-index upon assessment of hs-cTn in addition to assessment of conventional CVD risk factors. Reported findings generally demonstrated improvements in risk discrimination, with c-index changes in the region of 0.01 to 0.03 with the additional assessment of hs-cTn (**Figure 5**). Because some studies did not report confidence intervals for c-indices and their changes, it was not possible to conduct a quantitative meta-analysis of the c-index data.

Discussion

This systematic review and meta-analysis involving data from 16 prospective studies demonstrates a strong association between hs-cTn and the development of incident HF. The data suggest that individuals with a hs-cTn value in the top third of the population have a greater than two-fold increased risk of developing HF compared with individuals in the bottom third. This association was independent of conventional cardiovascular risk factors and natriuretic peptide levels, and consistent in the general population and high-risk groups, and in men and women. Assessment of hs-cTn in addition to conventional CVD risk factors improved risk discrimination quantified with the c-index, with study-specific estimates between 0.01 and 0.03. These data suggest that measurement of hs-cTn may enhance the ability to identify individuals at greater risk of developing HF. Hs-cTn troponin may be useful as a means of targeting echocardiographic screening for HF in high risk individuals to identify asymptomatic left ventricular dysfunction and allow early treatment (13), as has been studied for natriuretic peptides (38), although such an approach would require further evaluation.

Hs-cardiac troponin assays have been used in clinical practice in the diagnosis of myocardial infarction for some time and have recently been approved by the FDA for use in the United States (39). Elevated circulating cardiac troponin has been associated with worse clinical outcome in patients with acute decompensated HF (40) and chronic stable HF (41). The mechanisms triggering the release of circulating cardiac troponin in people without clinically manifest myocardial ischemia is unclear. It is speculated that contributing factors are underlying coronary artery disease, subendocardial ischemia, increased wall stress or left ventricular hypertrophy (25). Another possible mechanism is the cardiac stress characterized by activation of the renin-angiotensin and adrenergic systems, which has been studied in detail in patients with HF (42).

The studies contributing to our meta-analysis excluded individuals with symptomatic HF or a previous diagnosis of HF at baseline. However, some of them enrolled individuals with subclinical myocardial dysfunction at baseline, which tend to have a higher level of hs-cTn. Among participants with hs-cTnT (>8.8 ng/L) in the Multi-Ethnic Study of Atherosclerosis, 8.4% of men and 4.3% of women had a left ventricular ejection fraction <50%, and 18.2% of men and 27.7% of women had left ventricular hypertrophy assessed with cardiac magnetic resonance imaging (21). In the PEACE study involving patients with stable coronary heart disease, the prevalence of left ventricular ejection fraction between 40-50% was 14.4% in the whole cohort, increasing from 11.4% to 18.4% in the lowest to highest quartile of hs-cTnT (31). It should however be noted that the association of hs-cTn and incident HF was observed even after exclusion of individuals with left ventricular hypertrophy in the Cardiovascular Health Study (36).

Natriuretic peptides are the best-studied biomarkers in HF and strong predictors of prognosis in patients with established HF (43). A recent individual participant data meta-analysis of the association between natriuretic peptide levels and incident HF in the general population reported a risk ratio for individuals the top third versus the bottom third of 3.45 (2.66-4.46) (10). The magnitude of this association for natriuretic peptide is greater than that observed in our meta-analysis for hs-cTn, however those studies had not adjusted for hs-cTn. While individuals with hs-cTn tend to have higher natriuretic peptide levels (21,25,31), the magnitude of the Spearman correlation co-efficient was modest at 0.36 in the Cardiovascular Health Study (25). In studies that adjusted for natriuretic peptide in our analysis, the pooled hazard ratio was 2.08 (1.64-2.65), only a slight attenuation of the association without adjustment for natriuretic peptides of 2.39 (1.99-2.87). This suggests that hs-cTn has a strong association with incident HF

independent of natriuretic peptide levels. A literature based meta-analysis of 29 studies examining the association between hs-cTn and coronary heart disease and stroke reported risk ratios for the top versus bottom third of 1.59 (95% CI 1.38-1.83) for CHD and 1.35 (95% CI 1.23-1.48) for stroke (4). Thus the association between hs-cTn and HF is stronger than that for either CHD or stroke, a similar trend to that observed for NT-proBNP (10). With regards to improvement in risk discrimination, the C-index change with additional assessment of hs-cTn was lower than that previously observed for natriuretic peptides (0.01-0.03 vs 0.038) (10).

It has to be noted that the studies included in our meta-analysis relied on a single measurement of hs-cTn, whereas repeat measurements are likely to be more informative. In the Cardiovascular Health Study, in individuals with an elevated baseline hs-cTn, those with a further increase at follow-up had a higher HF risk compared with those with no change or a decrease in hs-cTn (25). This observation is in line with similar data from the ARIC study (37), suggesting that serial measurements of biomarkers may provide additional information over a single measurement. After developing a biomarker score based on concentrations of five biomarkers, including hs-cTn, investigators from the Framingham Heart Study observed a greater than 6-fold increase in the risk of HF in those with a score in the top quintile versus the bottom quintile (34). This score also improved discrimination and reclassification in terms of HF risk. Serial testing of biomarkers including hs-cTn and the use of multiple biomarkers simultaneously appears to hold promise, but is inevitably more resource intensive and costly.

Strengths and limitations

This systematic review has pooled data from sixteen studies reporting data from 67,063 participants with 4,165 HF events, giving significant statistical power. **This study adds to**

the existing literature in this field by providing an overview of all the available evidence regarding the association between hs-cTn and heart failure, with particular strengths including the thorough and comprehensive search strategy, transformation of study specific hazard ratios to a common scale to allow comparison and the high methodological quality of the included studies. There are however a number of limitations that merit discussion. There was significant heterogeneity observed in our analyses. No single factor was clearly demonstrated to account for a large proportion of this heterogeneity in meta-regression analyses and it is likely to be multifactorial. The assumption of a normally distributed exposure variable and a linear association with the outcome of interest may have been violated in some studies where individuals were categorized based on hs-cTn levels. A non-linear relationship could lead to an inflated hazard ratio after transformation, however there was no significant interaction between estimates from studies who modeled hs-cTn as a continuous or categorical variable. Finally, incomplete reporting of confidence intervals for C-index values prevented quantitative synthesis of this data and this element is descriptive only.

Given the potential for both clinical and methodological sources of heterogeneity in the included studies, collating individual-patient-level data from all of these studies would be valuable. This would allow standardization of outcome definitions and covariate adjustment. It would also allow for analysis of associations and assessment for effect modification in important subgroups and standardized assessment of the effect of adding hs-cTn to HF risk prediction models in terms of discrimination and calibration.

Summary

Serum hs-cTn is associated with the risk of incidence HF. The association equally applied to the general population and high-risk populations, and was independent of

conventional CVD risk factors and natriuretic peptide levels. Preliminary data showing discrimination improvements in HF risk with hs-cTn assessment suggest it may be a promising biomarker for measurement as part of primary prevention of HF.

Clinical perspective

People with higher levels of circulating cardiac troponin are at higher risk of developing new onset heart failure, after accounting for conventional risk factors and natriuretic peptide levels. Measurement of high sensitivity cardiac troponin improves the discrimination of heart failure risk. High sensitivity cardiac troponin may be useful in identifying individuals at high risk of heart failure to target preventive interventions.

Translational outlook

An individual-participant-data meta-analysis would help clarify the added value of high sensitivity cardiac troponin in the prediction of new onset heart failure, beyond conventional risk factors.

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Figure legends

Figure 1.

Search results and study selection process

Figure 2.

Forest plot for primary analysis of maximally adjusted hazard ratios for the association between hs-cTn and incident heart failure.

Heterogeneity: $I^2 = 79.9\%$ (95% CI - 68.1 - 87.3%). **Abbreviations:** NR=not reported, HR=hazard ratio. **Level of adjustment:** ‘++’= adjusted for demographics and CVD risk factors, ‘+++’= adjusted for demographics, CVD risk factors and natriuretic peptides.

Figure 3.

Hazard ratios for association between hs-cTn and incident heart failure by the degree of covariate adjustment.

Studies contribute to multiple levels if hazard ratios are reported at each level of adjustment. **Abbreviations:** NPs=natriuretic peptides (NT-proBNP or BNP), CVD=Cardiovascular disease. Comparisons are indirect as not all studies were included in analyses at each level of covariate adjustment.

Figure 4.

Meta-regression by categorical study level characteristics

Manner in which hazard ratios were reported in original paper. * P-value calculated using meta-regression. **Abbreviations – RCT=randomized controlled trial.

Figure 5.

Change in C-index with addition of hs-cTn by study

Table 1. Summary of included prospective cohort studies and baseline characteristics of participants

Study author	Study	Type of Study	Mean age	Female	Race	Hypertension	Diabetes	CVD (%)	Troponin	Follow up	Participants	HF events	Outcome	Follow up
		Population	(years)	(%)	(% White)	(%)	(%)		assay	(years)	(number)	(number)	definition	method
General population														
Brouwers 2014	PREVEND	General population	49	50	96	14	1	7	hsTnT (Roche)	13*	8569	374	All	RL ^{&}
De Filipi 2010	CHS	General population	73	60	NR	60	18	18	hsTnT(Roche)	12*	4221	1279	NF	SR, RL ^{&}
Eggers 2016	PIVUS	General population	70	50	NR	70	11	0	hsTnI (Abbott)	10^	864	67	All	RL
Ford 2016	WOSCOPS	General population ^a	55	0	NR	16	1	5	hsTnI (Abbott)	15^	3318	61	Hosp.	RL
Lyngbakken 2016	HUNT2	General population	47*	56	100	41	2	0	hsTnI (Abbott)	17*	9114	209	Hosp.	RL
McKie 2014	REP	General population	62	52	NR	28	7	12	hsTnT (Siemens)	11*	1843	193	All	RL
Neumann 2014	FINRISK	General population	48	50	100	45	5	0	hsTnI (Singulex)	14^	7899	505	NR	RL
Saunders 2011	ARIC	General population	63	59	78	45	15	0	hsTnT (Roche)	10*	9276	665	Hosp.	RL
Seliger 2017	MESA	General population	62	57	39	42	11	0	hsTnT (Roche)	12*	4986	177	Hosp.	SR ^{&}
Wang 2012	FHS	General population	59	53	NR	28	12	5	hsTnI (Singulex)	11 ^{\$}	3428	149	NF	RL ^{&}
High risk groups														
Bansal 2014	CRIC	CKD	58	46	43	NR	46	26	hsTnT (Roche)	6*	3483	320	Hosp.	SR, RL ^{&}
McQueen 2013	HOPE	High risk ^a	65	23	NR	42	35	94	hsTnT (Roche)	5 ^{\$}	2941	NR	All	Trial ^{&}
Okuyama 2017	Fujita	Hypertensive	69	29	0	100	43	20	hsTnI (Abbott)	7.2 ^{\$}	493	44	Hosp.	SR, RL
Omland 2009	PEACE	Stable CVD ^a	64	19	92	45	16	100	hsTnT (Roche)	5*	3679	104	Hosp, F	Trial
Scirica 2016	SAVOUR-TIMI-53	Diabetes ^a	65	33	80	82	100	0	hsTnT (Roche)	2*	2673	NR	Hosp.	Trial
Yiu 2014	CDATS	Diabetes	64	44	0	70	100	29	hsTnI (Abbott)	5*	276	18	Hosp.	SR, RL
Total			57	47	82	40	16	14		11	67,063	4,165		

*Median ^maximum \$mean ^anested in RCT. **Abbreviations:** NR=not reported, All=Fatal and non-fatal heart failure including hospitalization, NF=non-fatal heart failure, Hosp.=hospitalization for heart failure, F=fatal heart failure, RL=record linkage/medical record review, SR=self-report, Trial=active follow up within trial, &=endpoint adjudication performed, CKD=chronic kidney disease, CVD=cardiovascular disease, hsTnT=high sensitivity troponin T, hsTnI=high sensitivity troponin I. **Full study names:** PREVEND=Prevention of Vascular and Renal Endstage Disease, CHS=Cardiovascular Health Study, PIVUS=Prospective Investigation of the Vasculature in Uppsala Seniors study, WOSCOPS=West of Scotland Coronary Prevention Study, HUNT2=Nord-Trondelag Health Study, REP=Rochester Epidemiology Project, FINRISK=FINRISK study, ARIC=Atherosclerosis Risk in Communities, MESA=Multi-ethnic Study of Atherosclerosis, FHS=Framingham Heart Study, CRIC=Chronic Renal Insufficiency Cohort, HOPE=Heart Outcomes Prevention Evaluation, PEACE=Prevention of events with angiotensin converting enzyme inhibition trial, SAVOUR-TIMI-53=Saxagliptin Assessment of Vascular Outcomes Recorded with Diabetes Mellitus study, CDATS=Chinese Diabetic Heart Study.









